TRANSPLANTATION OF A PAIRED ORGAN, THE KIDNEY

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Transplantation of the kidney, at least between related donor-recipient pairs, is now a clinically feasible procedure. A recent analysis of more than 2000 human renal allografts reported to the Transplantation Registry indicated that the two-year survival rate for sibling donor-recipient pairs is approximately 80 per cent. The results of recent transplantations of cadaver kidneys shows a success rate comparable to that of open heart surgery for acquired valvular disease. I believe, therefore, that if a living, related donor is available, the results justify the transplantation of a kidney at an earlier stage than previously. Peripheral neuropathy and other irreversible consequences of advanced renal failure may thus be avoided.

A number of immunological problems, however, still exist. The agents now available for immunosuppressive therapy (azathioprine, prednisone, and antilymphocyte globulin therapy) are tools "not sharp enough" for the job. At present there is no evidence that antilymphocyte globulin has significantly improved the results of kidney transplantation in humans, although it is unquestionably a potent immunosuppressive agent in the experimental animal. Moreover, these agents cause serious side effects: infection, failure of wound healing, enhancement of the growth of malignant tumors which have been inadvertently transplanted, and an increase in the incidence of malignant tumors of the lymphatic system. This latter complication was most dramatically pointed up by a recent communication from the Cleveland Clinic noting the appearance of a reticulum cell sarcoma at the site of injection of antilymphocyte globulin.

Delayed damage to the renal allograft may also present serious problems. After a patient has apparently done well for a period of two or three years, the transplanted kidney may develop lesions of glomerular nephritis. In some cases this appears to be due to the development of the same disease that had destroyed the original kidneys of the recipient, while in other cases the lesions must be attributed to the rejection process. A dramatic illustration of the latter was a patient who developed typical lobular glomerulonephritis in a renal transplant without any history of renal disease. Allografting was necessitated in his case by the mistaken removal of a single ectopic kidney. Similar lesions also occur in the transplanted kidneys of normal rats. Enlargement and proliferation of endothelial and mesangial cells can be seen three to five days after transplantation. Glomerular capillaries are partially occluded at this time, and granular deposits of IgG and beta 1 C globulin on capillary walls and mesangial areas can be demonstrated by immunofluorescence. Deposits on the epithelial side of the basement membrane can be demonstrated by electronmicroscopy.

Another type of lesion, also related to rejection, may occur in kidney transplants that have functioned well for long periods. Obliterative vascular disease may develop without glomerular lesions. Again, a study of the sequential events in the rat kidney may help explain this result. Numerous mononuclear cells

may be found in the transplanted rat kidney within the peritubular capillaries. Later, small arterioles and venules may become involved with adherence of mononuclear cells to the vascular endothelium and enlargement of the endothelial cells. It seems probable that the basic process is antibody-mediated endothelial injury.

These findings emphasize the need for the early diagnosis and treatment of subclinical rejection. Immunologic damage to the vessels may not be apparent upon clinical examination, but may cause recurrent injury and scarring. Studies in the dog have demonstrated that the earliest effects of rejection may be evidenced by changes in the bloodflow long before there is any reduction in filtration rate or any rise in serum creatinine. Injury to vascular endothelium with resultant narrowing of the lumen causes a slowing of flow in the affected vessels, accumulation of platelets at sites of injury on the endothelium, precipitation of fibrin, and development of fibrosis. Theoretically, the vascular lesion could be prevented by agents that prevent fibrin deposition or platelet aggregation. Preliminary experiments in our own laboratory shows that aspirin, which prevents ATP-ase activated platelet aggregation, does indeed prolong the function of rat allografts. Further work along these lines is indicated.

Finally, a recent problem of significance is that of presensitization. Potential graft recipients may be presensitized by previous transfusions of blood containing white cells or platelets. In some but not all of these patients serum antibody, cytotoxic for human lymphocytes, may be demonstrated. Transplantation of a kidney into a recipient previously sensitized to antigens similar to that of the donor results in an immediate thrombosis of small vessels and cessation of renal function. Thus, in addition to selecting a recipient and donor of compatible tissue types, it is necessary before transplantation to test the cells of the donor directly against the recipient serum. This must be done as closely as possible to the time the transplant is to be performed; in one of our patients whose serum was negative for antibodies two weeks before transplantation, three blood transfusions just prior to transplantation apparently caused sensitization with resultant acute failure of the renal transplant. Several patients without demonstrable lymphocytotoxic antibodies in serum have also shown this phenomenon. It has been suggested that in these instances a test with monolayer cultures of donor cells might have demonstrated incompatibility. The problem of what to do with a potential recipient who has been sensitized by previous kidney transplants, and who now demonstrates antibodies against a large proportion of potential donors, is one of the current enigmas for which there is no present answer.

Thus, although analysis of two-year survival in kidney transplant recipients justifies this technique as a clinical procedure, a number of unsolved problems remain. Solutions to these must be found before we can consider kidney transplantation a definitive treatment for chronic renal failure.